Jaundice due to carbimazole

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SUMMARY On three occasions, a 63 year old housewife with hyperthyroidism developed a reaction which included fever, pruritus, malaise, and, on one occasion, jaundice one to 17 days after taking carbimazole. Challenge with carbimazole was followed within 12 hours by abdominal pain, pruritus, and increased serum transaminase levels. Light microscopy of a liver biopsy showed increase of portal zone cellularity over the control and the electron microscopy revealed fine structural changes compatible with drug-related liver injury.

Jaundice is a rare side-effect of several drugs used in the treatment of hyperthyroidism, including methimazole (Fischer *et al.*, 1973), thiouracil (Holoubek *et al.*, 1948), and propylthiouracil (Colwell *et al.*, 1952). Carbimazole (Neomercazole) has been in use for 23 years and is the most commonly prescribed antithyroid drug in the United Kingdom. Gastrointestinal and haematological side-effects are well-recognized with carbimazole but jaundice due to this drug has not been reported in the United Kingdom.

The following report describes a case of jaundice due to carbimazole. The history strongly suggested the diagnosis but ultimate confirmation depended on biochemical, histological, and ultrastructural studies after 'challenge' with the drug.

Case report

In June 1973, a 63 year old housewife was diagnosed as suffering from hyperthyroidism. She was given a therapeutic dose of I-131, propranolol 40 mg tds and carbimazole 5 mg tds. Two and a half weeks later, the patient noted fever, nausea, and aching in the legs. Five days later, she discontinued the drugs and the symptoms subsided.

In December 1973, the patient was first seen at

the Royal Free Hospital for consideration of further treatment. She had changed her physician and the referral letter did not include mention of the episode of fever in July, nor was this described by the patient. In February 1974, as she was again hyperthyroid, carbimazole 5 mg tds was prescribed. The next night, she experienced left hypochondrial pain and felt generally unwell the following morning. She also complained of pruritus of the hands. Her general practitioner noted jaundice and dark urine. Carbimazole was stopped. Gall stones were suspected but a cholecystogram performed 10 days later was normal.

Three weeks later, she took the drug again. Abdominal pain and pruritus of the hands and feet returned and after two days, she stopped the carbimazole and returned to the Royal Free Hospital. Physical examination now showed no abnormality. The liver and spleen were not enlarged. There was no jaundice, nor were there any other stigmata of liver disease.

Biochemical tests of liver function were aspartate transaminase (AsT 11 IU/l, alkaline phosphatase (SAP) 18 KAU/100 ml, and bilirubin 0.6 mg/100 ml). Serum proteins were normal. Blastic transformation of the patient's lymphocytes was not observed on exposure to carbimazole.

Percutaneous liver biopsy was performed. Light microscopy of the biopsy showed a mild mononuclear infiltration in the portal tracts. There was a mild fatty change, nuclear vacuolation, small clusters of mononuclear inflammatory cells, and grade 1 liver cell siderosis. Cholestasis and liver cell necrosis were not present. These changes were non-specific but consistent with a 'drug hepatitis'.

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ELECTRON MICROSCOPY: PRE-CHALLENGE

The 'pre-challenge' liver biopsy was unfortunately fixed initially in unbuffered 10% formalin. It was refixed in 3% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4, and then 1% osmium tetroxide in the same buffer. The tissue blocks were dehydrated and embedded in Epon 812. The ultra-thin sections were examined with Siemens electron microscope, Elmiskop 1. Although the fine structural preservation was unsatisfactory, the biopsy did provide sufficient information on the baseline appearance of the hepatocytes (Fig. 1). Notably, there was no proliferation of the smooth-surfaced endoplasmic reticulum (SER).

The patient was 'challenged' with 2×5 mg carbimazole. Although she remained asymptomatic with no pruritus, there was an abrupt alteration in the AsT which rose from 11 i.u./l to a maximum of 160 i.u./l 12 hours after the challenge (Table). The serum alkaline phosphatase did not change and the bilirubin level rose slightly.

	10 pm						
	28/2	7/3	11/3	12/3	13/3	14/3	15/3
Aspartate transaminase* (i.u./l)	17	11	160	87	36	17	14
Alkaline phosphatase (KAu/100 ml)	25	18	22	23	13	26	23
Bilirubin (mg/100 ml)	0.6	1.2	1.3	1.8	0.8	0.5	0.7

Table Effect of drug challenge on liver function tests

Normal range 4-15 KAu/100 ml.

*Normal range 4-15 i.u./l two days after previous dose of methimazole. Carbimazole 10 mg was given at 10 am on 11 March 1974.

Percutaneous liver biopsy was repeated 32 hours after the challenge. Light microscopy showed that there were no parenchymal changes. However, the portal tracts were larger and contained a moderate infiltrate composed mainly of histiocytes. A few areas of portal oedema, ductular proliferation and infiltration by segmented leucocytes were seen. There was no cholestasis.

Fig. 1 Electron micrograph of 'pre-challenge' liver biopsy showing considerable disarray and vesicular change of the endoplasmic reticulum. Glycogen rosettes can be seen in the cisternae of vesiculated granular ER, probably through the disrupted membrane (arrows). There are nine recognizable mitochondria with three of them (M) showing focal membrane change (arrow heads). These membrane changes of the endoplasmic reticulum and mitochondria are most likely fixation artefacts. Several microbodies (mb) are present. Uranyl acetate and lead citrate stain, $\times 26,500$.

Fig. 2 Electron micrograph of 'post-challenge' liver biopsy showing normal nucleus with nucleolus. The granular endoplasmic reticulum shows segmental dilatation of the lumen (X) associated with focal loss of ribosomes from the membrane (arrows). Uranyl acetate and lead citrate stain, $\times 18,000$.

Fig. 3 Electron micrograph of 'post-challenge' liver biopsy showing marked proliferation of smooth endoplasmic reticulum (SER). Two mitochondria show focal 'blister formation' (X) containing whorled membranous material. Uranyl acetate and lead citrate, $\times 20,000$.

Fig. 4 Electron micrograph of 'post-challenge' liver biopsy showing multiple autophagic vacuoles which contain dense and membranous material. Uranyl acetate and lead citrate, $\times 36,000$.

ELECTRON MICROSCOPY: POST-CHALLENGE

The 'post-challenge' liver biopsy was immediately fixed and processed as described previously.

Ultrastructurally (Figs 2, 3, and 4), the liver cells showed a marked degree of proliferation of smooth endoplasmic reticulum in the form of small round vesicles. In addition, there was segmental fusiform dilatation of the cisternae of the granular endoplasmic reticulum. The affected portion also showed myelin figure formation and loss of ribosomes from the membrane. Small autophagic vacuoles were common in the liver cells. Many mitochondria (estimated to be 10% of total population) showed a striking feature of 'blistering', as a portion of the mitochondrial membranes blew out and became undulant. The mitochondrial matrix in the affected region became electron light and contained occasional whorled myelin figures. There was a mild disarray of mitochondrial cristae. Mitochondrial granules were normal. Some bile canaliculi showed slight dilatation with loss of microvilli. A single small duct found in the specimen showed autophagic vacuoles in the ductal epithelial cells.

Discussion

Although many drugs used in the treatment of hyperthyroidism may occasionally cause jaundice, this would appear to be an extremely rare complication of therapy with carbimazole. There have, however, been seven documented cases in the American literature of jaundice due to methimazole, a popular antithyroid drug in the United States. Carbimazole, the 3-carbethoxy derivative of methimazole, is metabolized to methimazole in the body and it is surprising that jaundice due to carbimazole has not been reported from Great Britain, where the drug is widely used. Prost *et al.* (1973) in France recently described a patient who developed cholestatic jaundice while receiving carbimazole in a dose of 15 mg daily. Although drug challenge was not performed, the patient's lymphocytes showed mild lymphoblastic transformation when exposed to carbimazole.

Jaundice due to methimazole is usually associated with 'cholestatic' liver function tests and histological features on liver biopsy of cholestasis and non-specific infiltration of portal tracts with mono-

nuclear cells (Shipp, 1955; Martinez-Lopez *et al.*, 1962; Fischer *et al.*, 1973). However, Becker *et al.* (1968) described a patient with 'hepatitis' from methimazole with marked elevation of serum transaminase and histological evidence of focal hepatitis. Methimazole-induced jaundice appears to be a hypersensitivity reaction occurring in patients receiving normal doses of the drug. Hypersensitivity is also suggested by the occasional finding on liver biopsy of eosinophils infiltrating the portal tracts. Disappearance of jaundice and the return to normality of biochemical tests of liver function usually occur within two to three weeks but may be delayed up to 10 weeks (Fischer *et al.*, 1973). All these features of methimazole-induced jaundice are applicable to the patient we have described with jaundice due to carbimazole.

The ultrastructural changes on liver biopsy with methimazole-induced jaundice have not been described. In our patient some 32 hours after the drug challenge, fine structural abnormalities included hyperplasia of the smooth-surfaced endoplasmic reticulum, much focal cytoplasmic degeneration, and a peculiar membrane alteration in the endoplasmic reticulum and mitochondria. The mitochondrial changes were similar to those described in halothane hepatitis (Klion *et al.*, 1971). However, none of these changes can be considered specific and their relationship to the transient biochemical alterations needs further study. Because of the lack of a satisfactory preparation of the pre-challenge biopsy for ultrastructural examination, a proper comparative study on the post-challenge biopsy could not be made. A causal effect of the drug for the changes in the cell organelles cannot be ascertained. It must be borne in mind that the hepatic mitochondria in hyperthyroidism have shown some structural and functional alterations (Klion *et al.*, 1969). These mitochondria may be vulnerable to the changes of osmolarity, the ionic strength, and other physical properties of the fixatives, and the possibility of these changes representing fixation artefacts cannot be excluded.

The diagnosis of drug-induced jaundice is often circumstantial, with liver function tests and liver biopsy providing only suggestive evidence of a drug aetiology. In such cases an assessment of biochemical and histological changes after 'drug challenge' will usually provide valuable confirmatory evidence. Such challenges should be performed only under hospital in-patient conditions.

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